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PROCESS FOR THE PREPARATION OF 2-AMINO-3-PHENACYLBENZOXAZOLIUM HALIDES AND 2-AMINO-1-o-HYDROXYPHENYL-4-ARYLIMIDAZOLES

Inventors (72):	Annemarie [illegible], Herwig Pusch, Gerd Schlaak, DD
Applicant:	see (72)
Patent Holder:	see (72)
Agent:	Ernst-Moritz-Arndt-Universität Greifswald, RfN, 23 Greifswald, Domstrasse 20

Methods for the synthesis of heterocycles of the benzoxazole and imidazole series are described in the invention. These compounds are of interest as potential pharmaceutical agents and plant protective agents, or as optical brighteners, scintillators or substances for fluorescence

chromatography because of their fluorescent properties. A more rational synthetic method was required to be worked out for 2-amino-3-phenacylbenzoxazolium halides via the invention, and these compounds were required to be used as starting substances for a simple process for the synthesis of previously unknown imidazole derivatives.

2-amino-3-phenacylbenzoxazolium halides can be synthesized in good yields from 2-aminobenzoxazoles and α-haloketones by means of the melt process using a reaction time of 2 min with a large breadth of variation possibilities for the starting materials that are used. As a result of replacing the 2-amino-3-phenacylbenzoxazolium halides by amines, one obtains the previously unknown 2-amino-1-o-hydroxyphenyl-4-arylimidazoles of formula (see back of page).

Area of application of the invention

The synthesis procedure that is indicated in the invention relates to the synthesis of compounds which are of interest as potential medicinal drugs and plant protective agents and as intermediate products of such. As a consequence of their intense blue-violet fluorescence in solution and during UV irradiation of the solid substances, some of these compounds can be used as optical brighteners, scintillators or in fluorescence chromatography.

Characteristics of known technical solutions [to the problem in accordance with the invention]

2-Amino-3-phenacylbenzoxazolium halides were previously synthesized by heating 2-aminobenzoxazoles with α-haloketones in anethanolic solution. This procedure requires a reaction time of several hours and progresses with low yields, and can be carried out only with certain aromatic α-bromoketones (see A. Hetzheim, G. Köhler and H. Beyer, Z. Chem. 7, 186 (1967)).

The designated benzoxazolium halides and the other heterocyclic compounds that are capable of being synthesized from them are of interest as potential medicinal drugs and plant protective agents and, in the event of appropriate test results, they can be superior to previously used medications or plant protective agents in terms of their efficacy. However, the fact that the known preparation procedure takes place with an excessively low yield and too slowly is an impediment to industrial production.

Objective of the invention

The invention aims to develop a more economical process for the synthesis of 2-amino-3-phenacylbenzoxazolium halides and to indicate new routes for the syntheses of further practically usable heterocycles from these compounds.

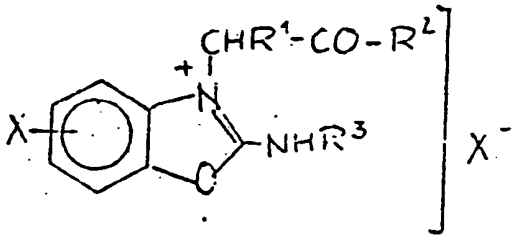
Disclosure of the essential features of the invention

- The technical problem which is solved by the invention

The technical problem for the invention is to discover a new process, which proceeds rapidly and with a large yield, for the synthesis of 2-amino-3-phenacylbenzoxazolium halides, and to achieve processes for the conversion of the products of the synthesis into other heterocyclic compounds.

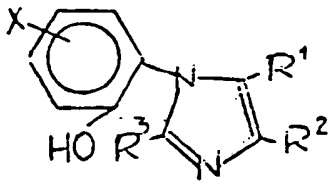
- Features of the invention

In accordance with the invention, 2-amino-3-phenacylbenzoxazolium halides of general formula



in which R^1 is hydrogen or an aryl group, R^2 is an aryl group, R^3 is hydrogen, an alkyl group, a cycloalkyl group, an aralkyl group or an aryl group and X is halogen, are obtained by reacting substituted 2-aminobenzoxazoles with aromatic α-haloketones in the melt using a reaction time of 1-2 min and processing with ethanol/ether as indicated in the examples of embodiments. The compounds that are synthesized in this way can be used directly for practical purposes, and they can also be processed further for other practical applications.

The 2-amino-3-phenacylbenzoxazolium halides are then suspended in dimethyl formamide and mixed with the corresponding amine and heated for 1-3 h under reflux. The colorless substances that are obtained after cooling and the addition of methanol are 2-amino-1-o-hydroxyphenyl-4-arylimidazoles of general formula:



in which R^1 is hydrogen or an aryl group, R^2 is an aryl group, R^3 is an alkyl group, a cycloalkyl group, an aralkyl group or an arylamino group or a nitrogen-containing heterocycle such as pyrrolidine, piperidine, morpholine, etc. They are recrystallized from the solvents that are indicated in the examples of embodiments.

Examples of embodiments

Example 1

2-Benzylamino-3-p-bromophenacylbenzoxazolium bromide

After thoroughly mixing together, 1.50 g (6.8 mmol) 2-benzylaminobenzoxazole and 1.86 g (6.8 mmol) p-ω-dibromoacetophenone are heated for 1-2 min in the melt with stirring. The melt, which is still warm, is then triturated with a small amount of ethanol; ether is added and filtration takes place. The colorless prisms can be purified by dissolving in ethanol and precipitating with [sic; from] ether.

Yield: 2.40 g (72%); melting point: 182-183°[C].

Example 2

2-Benzylamino-3-desylbenzoxazolium bromide

After thoroughly mixing together, 2.00 g (9.0 mmol) 2-benzylaminobenzoxazole and 2.48 g (9.0 mmol) desyl bromide are heated for 2 min at 150-160° with stirring. The melt that is obtained is taken up in ethanol and ether is added. Small colorless rods are obtained by reprecipitating from ethanol/ether.

Yield: 2.70 g (61%); Melting point: 254-256° (decomposition).

Example 3

2-n-Propylamino-3-p-bromophenacylbenzoxazolium bromide

After thoroughly mixing together, 1.50 g (8.5 mmol) 2-n-propylaminobenzoxazole and 2.40 g (8.5 mmol) p-ω-dibromoacetophenone are heated for 1.5 min at 130-140°. The melt which is obtained is triturated with a small amount of ethanol, and ether is added. The small shiny rods can be purified by reprecipitating from ethanol/ether.

Yield: 2.70 g (75%); melting point: 220-221° (decomposition).

Example 4

2-n-Propylamino-3-desylbenzoxazolium bromide

1.50 g (8.5 mmol) 2-n-propylaminobenzoxazole and 2.34 g (8.5 mmol) desyl bromide are thoroughly reduced in size and mixed together. The mixture is heated to 150° while stirring until a melt is obtained, and 2-3 mL ethanol are added. After the addition of ether and trituration, the colorless precipitate is filtered off and purified as described in Example 1.

Yield: 2.5 g (66%); melting point 261-263° (decomposition).

Example 5

2-Cyclohexylamino-3-p-bromophenacylbenzoxazolium bromide

1.50 g (6.9 mmol) 2-cyclohexylaminobenzoxazole and 1.95 g (6.9 mmol) p-ω-dibromoacetophenone are thoroughly mixed together and heated while stirring to 150° until melting takes place; the procedure is then followed as described in Example 1.

Yield: 2.40 g (70%); melting point: 225-226° (decomposition).

Example 6

2-Cyclohexylamino-3-desylbenzoxazolium bromide

A mixture comprising 1.50 g (6.9 mmol) 2-cyclohexylaminobenzoxazole and 2.40 g (8.6 mmol) desyl bromide are heated for 2 min at 130-140° until a melt is obtained. The product is taken up in ethanol and ether is added. The subsequent procedure is then analogous to Example 1.

Yield: 2.00 g (60%); melting point: 272-273° (decomposition).

Example 7

2-Amino-3-p-bromophenacyl-6-chlorobenzoxazolium chloride

A mixture comprising 1.00 g (5.9 mmol) 2-amino-6-chlorobenzoxazole and 1.65 g (5.9 mmol) p-ω-dibromoacetophenone is heated for 2 min at 130-140° while stirring until a melt is obtained. A small amount of DMF is added to it; the colorless crystals are filtered off and the

filtrate is mixed with ether. Recrystallization from DMF can be carried out for purification purposes.

Yield: 1.30 g (60%); melting point: 239-241°.

Example 8

2-n-Propylamino-1-o-hydroxyphenyl-4-bromophenylimidazole

1.5 mL of n-propylamine are added to 0.80 g (1.9 mmol) 2-amino-3-p-bromophenacylbenzoxazolium bromide which is suspended in 1.5 mL DMF. The solution is heated for 2 h under reflux, cooled and methanol is added. A colorless precipitate is formed after trituration. Small colorless rods are obtained by reprecipitating from DMF/methanol.

Yield: 0.70% g (97%); melting point: 246-248°.

Example 9

2-n-Propylamino-1-o-hydroxyphenyl-4,5-diphenylimidazole

0.70 g (1.8 mmol) 2-amino-3-desylbenzoxazolium bromide and 1.5 mL n-propylamine are heated for 1.5 h under reflux in 1.5 mL DMF. A copious amount of methanol is added to the solution, which has been slightly concentrated by evaporation. The colorless precipitate that is obtained is purified by reprecipitating from DMF/methanol. Solutions of this substance fluoresce intensely with a blue-violet color. The solid substance fluoresces under UV irradiation.

Yield: 0.50 g (76%); melting point: 279-281°.

Example 10

2-n-Butylamino-1-o-hydroxyphenyl-4,5-diphenylimidazole

0.70 g (1.8 mmol) 2-amino-3-desylbenzoxazolium bromide and 1.5 mL n-butylamine are heated for 1.5 h in 1.5 mL DMF under reflux and are then concentrated by evaporation. The subsequent procedure is then as in Example 9. The substance shows intense blue-violet fluorescence in solution.

Yield: 0.66 g (85%); melting point: 241-243°.

Example 11

2-Piperidino-1-o-hydroxyphenyl-4-p-bromophenylimidazole

1.00 g (2.4 mmol) 2-amino-3-p-bromophenacylbenzoxazolium bromide and 1 mL piperidine are heated for 1.5 h under reflux in 1.5 mL DMF. After cooling, methanol is added and trituration takes place; a colorless precipitate is formed. Recrystallization takes place from DMF/methanol.

Yield: 0.65 (67%); melting point: 204-205°.

Example 12

2-Morpholine-1-o-hydroxyphenyl-4-p-bromophenylimidazole

A mixture comprising 0.50 g (1.2 mmol) 2-amino-3-p-bromophenacylbenzoxazolium bromide and 1.5 mL morpholine is heated under reflux for 1 h in 1.5 mL DMF. A colorless precipitate is obtained after the addition of methanol and trituration; the precipitate is reprecipitated from DMF/methanol.

Yield: 0.75 g (77%); melting point: 230-231°.

Example 13

2-[1-(1-Methyl-2-hydroxy-2-phenyl)-ethylmethylamino]-4-p-bromophenylimidazole

0.50 g (1.2 mmol) 2-amino-3-p-bromophenacylbenzoxazolium bromide and 1.00 g (6.1 mmol) ephedrine are heated for 3 h under reflux in 1.5 mL DMF. After cooling, a copious quantity of methanol is added while triturating. The needles, which slowly crystallize out, can be purified by dissolving in a small quantity of DMF and precipitating from methanol.

Yield: 0.20 g (52%); melting point: 253-255°.

Example 14

2-Benzylamino-1-[2-hydroxy-4-chlorophenyl]-4-p-bromophenylimidazole

A mixture of 0.60 g (1.3 mmol) 2-amino-3-p-bromophenacyl-6-chlorobenzoxazolium bromide and 1.5 mL benzylamine is heated for 3.5 h in 1.5 mL of DMF under reflux. A colorless precipitate is formed by adding methanol; the precipitate is reprecipitated from DMF/methanol.

Yield: 0.35 g (57%); melting point: 267-269°.

Example 15

1-[2-Hydroxy-4-chlorophenyl]-2-morpholino-4-p-bromophenylimidazole hydrobromide

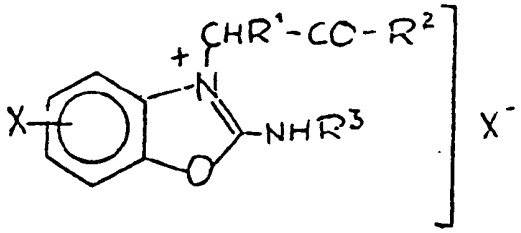
A suspension of 0.60 g (1.3 mmol) 2-amino-3-p-bromophenacyl-6-chlorobenzoxazolium bromide is heated in 1.5 mL DMF for 2 h under reflux after the addition of 1 mL morpholine.

The excess amine is evaporated. A colorless precipitate results from adding a copious quantity of ether and triturating. The needles are purified by dissolving in ethanol and precipitating from ether.

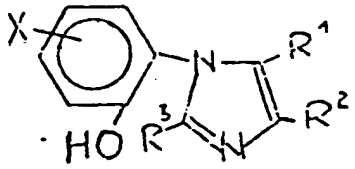
Yield: 0.45 g (68%); melting point: 214-216°.

Claim

Process for the preparation of 2-amino-3-phenacylbenzoxazolium halides and 2-amino-1-o-hydroxyphenyl-4-aryl-imidazoles, characterized in that 2-amino-3-phenacylbenzoxazolium halides of formula



in which R^1 is hydrogen or an aryl group, R^2 is an aryl group, R^3 is hydrogen, an alkyl group, a cycloalkyl group, an aralkyl group or an aryl group and X is halogen, are synthesized from the corresponding 2-aminobenzoxazoles and α-haloketones using the melt process, and the 2-amino-3-phenacyl-benzoxazolium halides that are obtained, with hydrogen for R^3, are reacted with amines to give 2-amino-1-o-hydroxyphenyl-4-arylimidazoles of formula:



in which R^1 can be hydrogen or an aryl group, R^2 can be an aryl group and R^3 can be an alkyl group, a cycloalkyl group, an aralkyl group, an arylamino group or a nitrogen-containing heterocycle such as pyrrolidine, piperidine, morpholine, etc.